ENDOSULFAN

RISK CHARACTERIZATION DOCUMENT

Executive Summary

(Major changes are marked in yellow and underlined on pages of iv - ix)

Department of Pesticide Regulation
California Environmental Protection Agency

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Introduction

The Department of Pesticide Regulation (DPR) conducts risk assessments for pesticides used in California to determine whether the use poses a present or potential human health hazard in California. Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations. This type of assessment includes a quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. After the completion of the risk assessment, the risk management phase takes place at DPR. Risk management refers to the process by which regulatory actions are chosen to deal with hazards identified in the risk assessment process. Risk managers consider scientific evidence and risk estimates, along with statutory, engineering, economic, social, and political factors, in evaluating alternative regulatory options and choosing among those options.

Risk assessments are mandated by the California Food and Agriculture Code (CFAC) Section 12824; the Birth Defect Prevention Act of 1984 (CFAC 13121-13135); and the Toxic Air Contaminant Act (CFAC 14021-14027). The Birth Defect Prevention Act of 1984 is often identified as Senate Bill 950 (SB 950), and the Toxic Air Contaminant Act is often identified as Assembly Bills 1807 and 3219 (AB 1807 and 3219). Under SB 950, the risk assessment is comprehensive and considers the potential exposures of various population groups, which may include workers, residents, and bystanders, depending on how the pesticide is used. Bystander is defined as any person not directly involved with the fumigation process, but is in the vicinity of the fumigation site. For each group, multiple routes of exposure, when appropriate, are assessed. These include inhalation via the air, absorption through the skin, and consumption of treated food. In comparison, AB 1807 and 3219 establish a procedure for identification and control of toxic air contaminants (TACs) in California. The statutes define toxic air contaminants as air pollutants that may cause or contribute to an increase in mortality or in serious illness, or that may pose a present or potential hazard to human health. DPR TAC program focuses on the evaluation and control of pesticides in ambient community air.

This report describes the risk assessment for the inhalation exposure to endosulfan in the products Drexel Endosulfan 3EC, Thionex® 3EC Insecticide, Gowan Endosulfan 50W, Thionex® 50W Insecticide, and Thionex® 50WSB Insecticide, under both SB 950 and AB 1807 mandates. In preparing this report, DPR staff reviewed pertinent scientific literature and reports through the spring of 2007. Based on the results of this comprehensive evaluation, the Director of DPR will determine whether endosulfan is a TAC, and whether mitigation measures are needed to reduce the exposure of workers and the general population in California. If endosulfan is designated a TAC, the risk management provisions of the law mandate the DPR to determine the need for and develop appropriate control measures for endosulfan uses in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), the Air Resources Board, the air pollution districts, air quality management districts, and county agricultural commissioners of the affected counties.

What is contained in the report?

This report evaluates the potential for endosulfan exposure and includes: A review of the available scientific evidence on endosulfan and its degradation product (α-endosulfan, β-endosulfan, and endosulfan sulfate) regarding their physical and chemical properties, sources in the environment, and fates in the environment; estimates of human exposure to airborne endosulfan; summary of toxicology studies conducted with endosulfan; and an assessment of the risk to humans resulting from current or anticipated exposure to airborne endosulfan.

What is endosulfan, what are the primary sources of endosulfan in the environment, and how it is used?

Endosulfan is a pesticide belonging to the chemical family of organochlorine, sub-class chlorinated cyclodiene and containing only one double bond. Its chemical formula is $C_9H_6Cl_6O_3S$ with a molecular weight of 406.96 g/mole. The molecular structures have two stereochemical isomers, α- and β-endosulfan. The end-use product of endosulfan is a mixture of two isomers, typically in a 2:1 ratio. Pure endosulfan is a colorless crystal; but technical grade is brown in color, and similar to hexachlorocyclopentadiene, sometimes mixed with sulfur dioxide in odor. Endosulfan is relatively poorly soluble in water with solubility of 0.33 mg/L at 25 ^oC, but readily soluble in common organic solvents. It is moderately volatile to air and adsorptive onto soil particles. The vapor pressure is $3.0x10^{-6}$ for α-endosulfan and $7.2x10^{-7}$ mm Hg (25 ^oC) for β-endosulfan. The corresponding Henry's Law Constant is $4.9x10^{-6}$ for α-endosulfan and $1.2x10^{-6}$ atm-m^3/mol for β-endosulfan. The adsorption coefficients (Koc) were estimated to be 10600 and 13600 cm^3/g for α- and β-endosulfan, respectively.

The primary source of endosulfan in the environment is almost exclusively from pesticide application. There are no known natural sources of endosulfan. It is a broad-spectrum non-systemic insecticide and acaricide with contact and stomach action. It is used to control sucking, chewing, and boring insects on a wide variety of vegetables, fruits, grains, cotton, and tea, as well as ornamental shrubs, vines, and trees. Currently, there are six registered products containing active ingredient of endosulfan in California. Five of them are end use insecticide products in formulations of emulsifiable concentrate, wettable powder, or wettable powder in water soluble bags. The other one is technical grade endosulfan which is solely used for formulation into end use products. The labels all bear signal word "DANGER-POISON".

Endosulfan is applied through irrigation systems (chemigation), groundboom sprayer, airblast sprayer, rights-of-way sprayer (in maintenance of landscaped areas adjacent to roads, highways, power lines, telephone lines, canals, railroads or other similar sites), low-pressure handwand sprayer, high-pressure handwand sprayer, backpack sprayer, fixed-wing aircraft, and dip treatment for germinating seed, seedling, bare root, and other commodities. Endosulfan is compatible with many other pesticides and may be found in formulations with dimethoate, malathion, methomyl, monocrotophos, pirimicarb, triazophos, fenoprop, parathion, petroleum oils, and oxine-copper. It is not compatible with alkaline materials because it is vulnerable to hydrolysis.

Endosulfan use in California decreased from 238,635 pounds in 1997 to 83,242 pounds of active ingredient in 2005. Both total pounds used and acreages applied in 2005 were almost 1/3 of those in 1997. However, the use patterns, frequency distribution for pounds used, acres applied, and application rates of individual endosulfan application, were similar compared 1997 to 2005. The use decrease was mainly due to reduction of cotton crop in the Central Valley. The six top use counties were Fresno, Kings, Imperial, Kern, Tulare, and Riverside. The peak use months were from June to September. For the six top use counties, the peak use months were June to August in Fresno; June and July in imperial; August and September in Kern; June to September in Kings; May to August in Riverside; and July to September in Tulare counties. Endosulfan was mainly used on cotton, alfalfa, lettuce, tomato, melons, grapes, and various vegetables in California.

What is the fate of endosulfan in the environment?

Endosulfan can be found in almost all media in the environment and all over the world. The α-isomer is more volatile and dissipative, while the β-isomer is generally more adsorptive and persistent. Its overall moderately volatile property enables it to be transported as vapor and spray drift to multiple media, while its moderate adsorption and persistence properties enable it to stay in the environment for an extended period and can be transported via runoff to surface water bodies or via dust dispersion to atmosphere and redeposit to different areas. Therefore, endosulfan has been detected in areas where it was not used, *e.g.*, the Lake Tahoe Basin and the Sequoia National Park in California, and even in the Arctic. Photolysis and subsurface leaching are negligible.

Endosulfan degradation can be via abiotic or biotic processes in aerobic and anaerobic conditions. Oxidation and hydrolysis are the main routes for endosulfan degradation. Both α- and β-endosulfan can be oxidized to endosulfan sulfate via biotic metabolism. Endosulfan sulfate is of comparable toxicity as its parents and more persistent with half-life of 100-2148 days, two or more times longer than its parents. Estimated half-lives for α- and β-endosulfan in different soils and other environmental conditions ranged 19-124 and 42-265 days respectively, and those for the combined toxic residues (α- and β-endosulfan plus endosulfan sulfate) ranged from 9 months to 6 years. They all can, when in water, hydrolyze abiotically or biotically to endosulfan diol. Endosulfan diol is more hydrophilic and less toxic. Hydrolysis is favored in neutral to alkaline media. At 25 ^{o}C estimated half-lives of α- and β-endosulfan were 11 and 19 days at pH 7, and 4 and 6 days, respectively, at pH 9. However, at pH 5, they were more than 200 days for both α- and β-endosulfan.

Who will be exposed to endosulfan, and what are the exposure levels?

In addition to those involved with the application of endosulfan, individuals might be exposed to endosulfan if they live, work, or perform other activities adjacent to fields that are being treated or have recently been treated (bystander exposure). Air monitoring studies in Fresno, Monterey, and Tulare counties suggest that endosulfan exposures to the public are possible from airborne residues that have moved away from a pesticide application. In considering potential ambient exposures, it is reasonable to assume that the greatest potential exists for those individuals closest to the application site in time and distance. On this basis, the exposure assessment for endosulfan assumes that bystander exposure represents the highest potential for ambient exposure to the public.

In this report, exposures are expressed as absorbed doses, which account for differences in the age-related inhalation rate and in the exposure duration under the various scenarios. Exposure durations are short-term (i.e., intervals of 7 days or less), seasonal (intermediate-term intervals, lasting from 1 week to 1 year) and annual. For bystanders, the exposures are primarily short-term, although seasonal and annual exposures are possible for individuals living and working adjacent to multiple tomato and potato fields.

Bystander exposures to airborne endosulfan were estimated using data from air monitoring conducted 6 – 16 m from the edges of a San Joaquin County apple orchard during an application of endosulfan. The estimated short-term absorbed daily dosage (STADD) of bystanders to endosulfan is 0.00160 mg/kg/day for infants and 0.00076 mg/kg/day for adults. Seasonal exposure and annual exposure durations were estimated to be 1 month, as repeated applications adjacent to any one individual are considered unlikely for longer intervals. The estimated seasonal average daily dosage (SADD) is

0.00056 mg/kg/day for infants and 0.00027 mg/kg/day for adults. The estimated annual average daily dosage (AADD) is 0.000047 mg/kg/day for infants and 0.000022 mg/kg/day for adults.

What are the potential health effects from acute and repeated exposures to endosulfan?

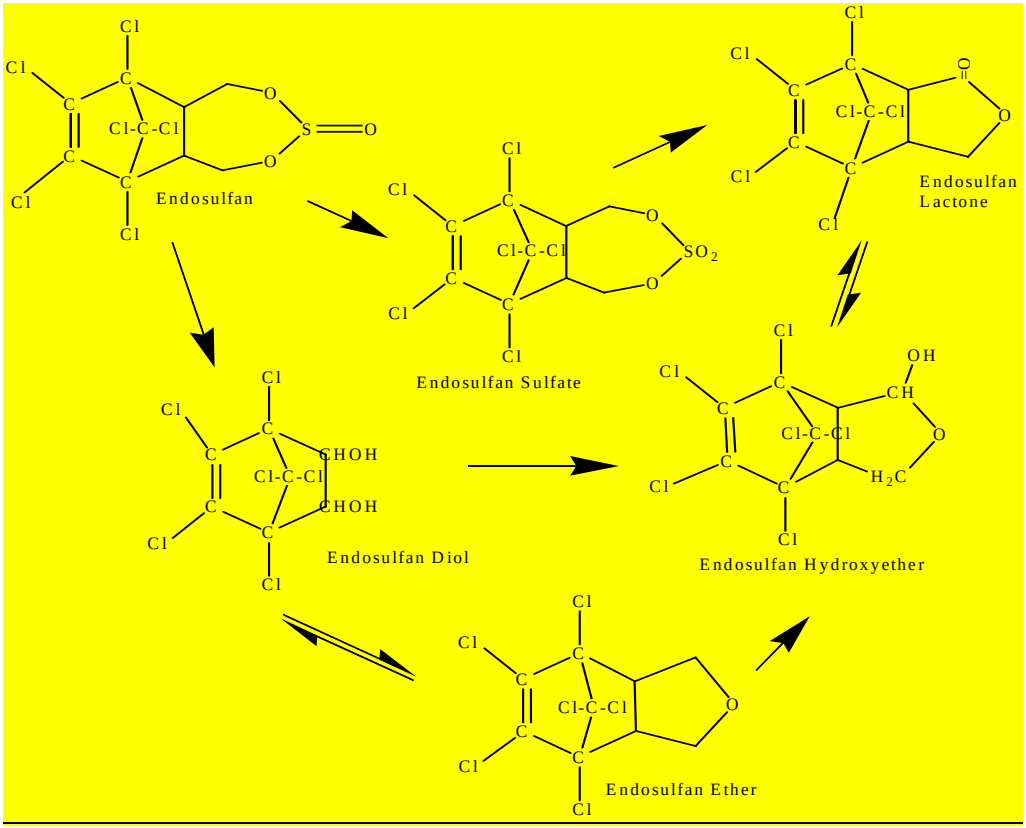
BIOTRANSFORMATION (Figure 1)

Endosulfan modifies the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione (GSH) in rat liver, lung and erythrocytes when administered via aerosol, thereby potentially contributing to oxidative stress in some tissues.

Stereoselective endosulfan sulfate formation from human recombinant P450s showed that α-endosulfan is mediated by CYP2B6, CYP3A4 and CYP3A5 and β-isomer by CYP3A4 and CYP3A5.

Endosulfan affected glutathione (GSSG), glutathione peroxidase (GPX), reductase (GTR) and S-transferase (GST) activities. GSSG and GPX were increased, and GTR and GST were decreased after treatment.

Figure 1. Proposed Metabolic Pathway in Rat and Sheep for Endosulfan (Dorough, et al., 1978; Gorbach et al., 1968; Bebe and Panemangatore, 2003; Lee et al., 2006) Phase I reactions on endosulfan are performed with P450s: CYP2B6, CYP3A4 & CYP3A5; Phase II reaction is with GST; Other enzymes involved with endosulfan metabolism are antioxidants: SOD, GPX and CAT



TOXICOLOGY

Acute Inhalation NOEL

An acceptable acute inhalation exposure study was not available to obtain an acute inhalation NOEL. However an acceptable subchronic rat inhalation (the only one acceptable by FIFRA Guidelines) study with a NOEL of 0.0010 mg/L (0.194 mg/kg/day) was used to calculate the potential for acute single-day inhalation exposure to workers, and for exposure to endosulfan in ambient air or to bystanders. In this study, endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29-day recovery. The NOEL for inhalation was based on emaciation, pale skin, squatting position and high-legged position, decreased bodyweight gain and food consumption, increased water consumption, and clinical chemistry parameters (reversed during recovery). The NOEL of 0.194 mg/kg/day is lower than the oral NOEL of 0.7 mg/kg/day from the rabbit developmental study and more importantly, it is route-specific. The study was therefore selected as the definitive study for the critical inhalation NOEL of 0.0010 mg/L (0.194 mg/kg/day). This NOEL was used to estimate the margin of exposure (MOE) for acute inhalation (occupational and (non-occupational) bystander exposure).

Subchronic Inhalation NOEL

The definitive study for subchronic inhalation exposure was a study performed in the rat, where endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29 day recovery. The NOEL for inhalation was 0.0010 mg/L based on emaciation, pale skin, squatting position and high-legged position, decreased bodyweight gain and food consumption, increased water consumption, and clinical chemistry parameters (reversed during recovery). This study was acceptable according to FIFRA Guidelines and was the only study available for evaluation of endosulfan exposure by inhalation. It was therefore selected as the definitive study for the critical inhalation NOEL of 0.0010 mg/L (0.194 mg/kg/day) to estimate the MOE for seasonal (non-occupational) bystander exposure.

Chronic Inhalation NOEL

An acceptable chronic inhalation exposure study was not available to obtain a chronic inhalation NOEL. Therefore, an acceptable subchronic rat inhalation study with a NOEL of 0.0010 mg/L (0.194 mg/kg/day) was used to calculate the potential for chronic inhalation exposure to workers, and for exposure to endosulfan in ambient air or to bystanders. In this study, endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29-day recovery. The NOEL for inhalation was based on emaciation, pale skin, squatting position and high-legged position, decreased bodyweight gain and food consumption, increased water consumption, and clinical chemistry parameters (reversed during recovery). A 10x uncertainty factor for extrapolation from subchronic to chronic was applied to the NOEL of 0.194 mg/kg/day to give a final critical ENEL of 0.0194 mg/kg/day. This dose is lower than the chronic oral NOEL of 0.57 mg/kg/day from the chronic dog dietary study and more importantly, it is route-specific. The study was therefore selected as the definitive study for the critical ENEL of 0.0194 mg/kg/day. This NOEL will be used to estimate the MOE for chronic occupational and (non-occupational) ambient air and bystander exposure.

Neurotoxicity

Neurotoxicity is the primary effect observed both acutely and chronically in both humans and animals (where clinical signs were recorded). Documented human data have shown the central nervous system

to be the major target of endosulfan action. Endosulfan is a strong neurotoxin in animals (rats, dogs, mice, cows, cats, goats and sheep) as well as in humans.

Endocrine disruption

Although endosulfan has effects in the male reproductive system as has been described in this document, doses that would protect for neurotoxicity and other systemic effects would also protect for endocrine disruption (observed only at higher doses). While there were no inhalation studies performed where fetuses, pups or neonates were exposed, all data from the acceptable rat inhalation study indicated that young adolescent/adults (age 7-9 week) show systemic toxicity in the absence of histopathological effects to any reproductive organs in either sex. The No Observed Effect Level (NOEL) for inhalation (0.194 mg/kg/day) is considered protective of all age groups and data do not warrant the use of additional uncertainty factors at this time.

TARGET ORGANS

The nervous system, liver and kidney are primary target organs. Endosulfan induces xenobiotic metabolizing enzymes.

In FIFRA Guideline acceptable animal studies, endosulfan did not result in developmental or reproductive effects in adults, fetuses, neonates or young adults.

Is there any potential cancer risk from exposure to endosulfan?

Hepatocyte gap junctional intercellular communication was inhibited by endosulfan, as well as by the sulfate, lactone and ether metabolite. Gap junctional intercellular communication was also inhibited by both α- and β - isomers in primary Sprague-Dawley rat hepatocytes, as well as WB-F344 rat liver cell lines. While gap junctional intercellular communication might be considered to be a tumor promotional event, all studies reported were performed *in vitro*. In studies performed *in vivo* there has been no evidence to indicate that endosulfan is a tumor promotor.

For genotoxicity, numerous studies have been performed in bacteria, yeast, mammalian cells in culture and *in vivo* in laboratory animals. Both positive and negative results have been reported. There is some evidence for genotoxicity with endosulfan, especially in tests for chromosomal effects. However, in order to identify a positive effect *in vivo*, animals were treated at doses that exceed the maximally tolerated dose (MTD). Mortality would occur at the MTD thereby preventing tumor development through early death.

When considering the results of all available *in vivo* studies performed in rats and mice, there is insufficient evidence indicating endosulfan is oncogenic in the studies conducted to date. There were acceptable studies with well designed, peer reviewed protocols performed in rat (104 week chronic/oncogenicity) and in mouse (18 month) that resulted in no indication that endosulfan is oncogenic. Endosulfan is categorized as “A4” (not classifiable as a human carcinogen) by the American Conference of Governmental Industrial Hygienists (Substances and Physical Agents and Biological Exposure Indices, Cincinnati, OH, 2005). USEPA states: "Cancer Determination: The carcinogenicity issue has been considered by the Health Effects Division--Cancer Peer Review Committee. The Committee agreed that 'there was no evidence of carcinogenicity' for endosulfan" Endosulfan is placed in Group E: Evidence of non-carcinogenicity for humans (Revision of Occupational and Residential Exposure/Risk Assessment for the Endosulfan Reregistration Eligibility Decision Document (RED); Revised; Docket number: EPA - HQ- OPP- 2005 - 0459). The Canadian

Preliminary Risk and Values Assessment for Endosulfan states "Endosulfan was not carcinogenic in mice or rats and was not genotoxic," (PMRA, 2007).

Does the concentration of endosulfan in the air pose a potential health hazard for humans?

The risk for non-carcinogenic health effects can be expressed as a margin of exposure (MOE), which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human populations and the sensitive subgroup.

Compounds, such as endosulfan that may exceed health protective levels in the air, qualify for listing as a TAC. Consideration as a possible TAC applies an additional 10x factor to the RfC, meaning that an MOE of less than 1000 would meet the criterion for identification as a TAC. Potential for differing levels of exposure between infants and adults is factored in by use of the respective breathing rates for adults and children to calculate the RfCs.

AIR EXPOSURES TO BYSTANDERS at APPLICATION SITES

STADD: Short term MOEs for non-dietary infant and adult bystander scenarios were greater than 100, ranging from 121 to 255 for infant and adult, respectively. It must be noted that since the bystander, infant scenario has an MOE of less than 1000 endosulfan may be listed as a potential toxic air contaminent (California Food and Agricultural Code: 14021-14027).

SADD: Seasonal exposure MOEs for the infant and adult bystander air scenarios were greater than 100 (346 and 719, respectively). Note that since the bystander scenarios have MOEs of less than 1000, endosulfan may be listed as a potential toxic air contaminant (California Food and Agricultural Code: 14021-14027).

AADD: All annual exposure MOEs for the infant and adult bystander scenarios were less than 1000 (413 and 882, respectively).

Conclusion

DPR recommends that endosulfan be considered for listing as a TAC.